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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,617	GODDARD ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0505,0705*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 05/02/2005 has been entered. Claims 4-8, 11-17 are pending and being examined.

Inventorship

In view of the papers filed 05/02/2005, the inventorship in this nonprovisional application has been changed by the deletion of Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Wantanabe.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC §§ 101, 112

Claims 4-8, 11-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants argue that utility need not be proved to an absolute certainty and that a correlation between the evidence and the asserted utility is sufficient; that the accepted understanding in the art is that there is a correlation between gene expression and the level of the encoded protein; that it is Applicants' position that a change in gene expression establishes a significant probability that the encoded polypeptide will also be changed; that the legal standard for demonstrating utility is more likely than not, and that the standard is not absolute certainty; and, that it is more likely than not that those skilled in the art would believe that the PRO1753 polypeptide is useful as a diagnostic tool for cancer.

Applicant's arguments have been fully considered but they are not persuasive. The present rejection is not based upon "an absolute certainty," "statistical certainty," "absolute predictability," "an invariable exact correlation," or a universal correlation. The present rejection is based upon Applicants' failure to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The M.P.E.P. reminds Office personnel that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. As noted by applicants, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." The examiner has cited countervailing evidence to show that the skilled artisan would have a reasonable, legitimate basis to doubt the utility of the PRO1753 polypeptide because the skilled artisan recognizes that protein levels are not always consistent with mRNA levels. The evidence, considered as a whole, provides a reason for one skilled in the art to question the objective truth of the statement of diagnostic or therapeutic use of the PRO1753 polypeptide. In the absence of any information on the role, activity, or expression of the PRO1753 polypeptide in cancer, the examiner therefore considers the asserted utilities to not be specific and substantial because the skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer.

The examiner disagrees with Applicants' characterization of the utility guidance provided by M.P.E.P. § 2107.01 III because unlike the situation wherein a claimed compound has been

tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, in the present situation Applicant's have not provided any testing of the expression, role, or activity of the PRO1753 polypeptide.

The examiner also disagrees with Applicants reliance on "[t]o violate [35 U.S.C.] 101 the claimed device must be totally incapable of achieving a useful result" because based on the factual record of this case, there is no evidence that the claimed invention will function as a cancer diagnostic or therapeutic and the evidence, considered as a whole, provides a reason for one skilled in the art to question the objective truth of the statement of diagnostic or therapeutic use of the PRO1753 polypeptide.

The examiner also disagrees with Applicants' reliance on the caveat in Example 12 of the utility guidelines as a defense against a lack of utility because unlike the situation wherein the specification discloses that receptor A is present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells, in the present case Applicants have not provided any testing of the expression, role, or activity of the PRO1753 polypeptide.

Regarding other patents claiming differentially expressed polypeptides that the Office may have issued, as Applicants' recognize each case must be decided on its own merits based on the evidence of record. Furthermore, the present case Applicants have not provided any testing of the expression, role, or activity of the PRO1753 polypeptide.

As noted by Applicants, "testing is often required to establish practical utility." In the present case, the specification does not provide any testing of the level of expression, activity, or role in cancer of the PRO1753 polypeptide. In the absence of this testing, in the presence of evidence that protein levels are not always consistent with mRNA levels, and considering the

totality of the evidence, there is no basis for concluding that the skilled artisan would be convinced that it is more likely than not that the PRO1753 mRNA, polypeptide, and antibody could be used for the diagnosis or treatment of cancer. In contrast to situations where in vitro testing of a novel pharmaceutical compound was sufficient to establish practical utility, the present specification does not provide any testing of the level of expression, activity, or role in cancer of the PRO1753 polypeptide.

Applicants argue that they have established that the gene encoding the PRO1753 polypeptide is differentially expressed in certain cancers compared to normal tissue and is useful as a diagnostic tool, and therefore the corresponding polypeptide and antibodies are useful as diagnostic tools, as evidenced by the paragraphs 6 and 7 of the Grimaldi declaration (Exhibit 1). Applicants argue that the precise level of expression, the activity, or role of the PRO1753 polypeptide in cancer is irrelevant, and that the resolution of these issues is not required in order to use the disclosed polynucleotides and polypeptides as diagnostic tools, as evidenced by paragraph 7 of the Grimaldi declaration (Exhibit 1). Applicant's arguments have been fully considered but they are not persuasive. The declaration of J. Christopher Grimaldi under 37 CFR 1.132 filed 05/02/2005 (Exhibit 1) is insufficient to overcome the rejection of Claims 4-8, 11-17 based upon a lack of utility as set forth in the last Office action because: Declarant argues that it was determined whether the polynucleotides tested were more highly expressed, less expressed, or whether expression remained the same, and that it is reasonable to assume that any detectable differences will represent at least a two fold difference in cDNA. Declarant argues that the results of these gene expression studies can be used to differentiate tumor from normal, and that the precise levels of gene expression are irrelevant. Declarant argues that if a difference

is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes. Declarant's arguments have been fully considered but they are not persuasive. The expression of all polynucleotides or polypeptides from a tumor sample or any other sample can invariably be classified as either increased, decreased, non-existent, or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are expressed in this manner can be used to detect or characterize the tumor or other sample. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility. Furthermore, no information is provided in the differential analysis of PRO1753 polynucleotide expression regarding the level of expression, activity, or role in cancer of the PRO1753 polypeptide. The examiner has cited evidence to show that protein levels are not always consistent with mRNA levels and that protein expression levels are not predictable from the mRNA expression levels. The present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. This evidence shows that the skilled artisan would have a legitimate basis to doubt the utility of the PRO1753 polypeptide. The skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer. Therefore, the disclosure that DNA68883-1691 is differentially expressed in certain cancers compared to normal tissue does not impute a specific, substantial, and credible utility to the PRO1753 polypeptide. The examiner is not saying that Applicants must disclose the activity or role in cancer of the PRO1753 polypeptide. The examiner is saying that Applicants have not provided any information in the present specification regarding the level of expression, activity,

or role in cancer of the PRO1753 polypeptide. Based on the present disclosure, one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

Applicants argue that Hu (J Proteome Res. 2003 Jul-Aug;2(4):405-12) does not teach that genes, and their corresponding proteins, with a less than five-fold change in expression are not important or cannot be used as molecular markers of disease, as demonstrated by the fact that ER-negative tumors did not show a correlation. Applicants argue that genes and polypeptides with lower levels of change in expression can nonetheless still be used as diagnostic tools whether or not they are good targets for further research. Applicant's arguments have been fully considered but they are not persuasive. In the present case, the specification provides data showing a qualitative difference in PRO1753 mRNA levels between esophageal tumor and normal esophagus. PRO1753 mRNA was more highly expressed in esophageal tumor as compared to normal esophagus. However, there is no evidence regarding the expression, role or activity of the PRO1753 polypeptide. Since the present claims are directed to the PRO1753 polypeptide, it is reasonable to consider whether the skilled artisan would have a reasonable basis to question the asserted utilities of the PRO1753 polypeptide based solely on the differential analysis of PRO1753 mRNA expression. Hu was cited as countervailing evidence to show that the significance of the disclosed analysis of PRO1753 mRNA expression in relation to PRO1753 polypeptide expression in cancer diagnosis or treatment is unknown. Firstly, the skilled artisan recognizes that in differential display analysis of mRNA expression there are biologically relevant results as well as biologically irrelevant results. See Hu (J Proteome Res.

2003 Jul-Aug;2(4):405-12), which teaches that "[h]igh-throughput technologies, such as proteomic screening and DNA micro-arrays, produce vast amounts of data requiring comprehensive analytical methods to decipher the biologically relevant results" (Abstract). "In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (page 405, left column, full paragraph 1). Implicit in these teachings is that there are also biologically irrelevant results, and that further research is required in order to determine which results are biologically relevant. One skilled in the art would not know if the disclosed PRO1753 mRNA expression is significant or insignificant, relevant or irrelevant. The present specification fails to disclose enough information about PRO1753 mRNA expression to make its usefulness immediately apparent to those familiar with the technological field of the invention. Secondly, the present specification provides no information regarding the level of expression, role or activity of the PRO1753 polypeptide in tumors. The present specification provides no information with which to determine whether PRO1753 mRNA or polypeptide expression in tumors is important or is attributable to tumor-independent differences between samples. The skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer. Consequently, the skilled artisan would have a legitimate basis to doubt the utility of the PRO1753 polypeptide for either cancer diagnosis or treatment.

Applicants argue that nothing in Wang (Trends Pharmacol Sci. 1996 Aug;17(8):276-9) is contrary to Applicants' assertion that the differentially expressed genes and their associated polypeptides can be used as cancer markers. Applicants argue that they have completed the equivalent of steps 1-9 of the ten steps outlined by Wang in Figure 1. Applicant's arguments

have been fully considered but they are not persuasive. The examiner can accept, for arguments sake, that gene expression analysis, tools or techniques have the potential for the discovery of new diagnostic or therapeutic targets. However, in the present case no information is provided in the differential analysis of PRO1753 mRNA expression regarding the level of expression, activity, or role in cancer of the PRO1753 polypeptide. The examiner does not agree that such a disclosure provides a "specific benefit in currently available form." This further characterization is part of the act of invention and until it has been undertaken, Applicants' invention is incomplete. The examiner also disagrees with Applicants' assertion that they have completed the equivalent of steps 1-9 of the ten steps outlined by Wang in Figure 1 because the present specification does not provide any information regarding the target validation of the PRO1753 polypeptide.

Applicants argue that the skilled artisan would be more likely than not to believe that the PRO1753 polypeptide could be used as a diagnostic tool for cancer. Applicant's arguments have been fully considered but they are not persuasive. The examiner has cited countervailing evidence to show: firstly, that the significance or relevance of the disclosed PRO1753 mRNA expression in relation to cancer diagnosis or treatment is unknown; secondly, that protein levels are not always consistent with protein levels. Furthermore, the present specification provides no information regarding the level of expression, role or activity of the PRO1753 polypeptide in tumors. The present specification provides no information with which to determine whether PRO1753 mRNA or polypeptide expression in tumors would be important or would be attributable to tumor-independent differences between samples. One skilled in the art would not know if or how PRO1753 polypeptide expression would change in cancer. In the presence of

evidence that the significance or relevance of PRO1753 mRNA expression in relation to cancer diagnosis or treatment is unknown, in the presence of evidence that protein levels are not always consistent with mRNA levels, and in the absence of any testing of the level of expression, role or activity of the PRO1753 polypeptide in tumors, the examiner concludes that there is no basis for concluding that the skilled artisan would be convinced that it is more likely than not that the PRO1753 mRNA, polypeptide, or antibodies could be used for the diagnosis or treatment of cancer.

Applicants argue that it is not clear that Haynes even supports the examiner's position because Haynes did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein, because Haynes did report a general trend with some exceptions, because Gygi reports a strong correlation between increasing mRNA levels and increasing protein levels, and because Haynes did not show that there is a universal lack of a correlation between mRNA and protein levels. Applicants' arguments have been fully considered but they are not persuasive. Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution) discloses that DNA68883-1691 is more highly expressed in esophageal tumor as compared to normal esophagus (page 143). Applicants assume that the DNA68883-1691 transcript levels are indicative of the levels of PRO1753 protein expression. However, there is no evidence regarding the expression, role or activity of the PRO1753 polypeptide. Haynes was cited as providing evidence that protein expression levels are not predictable from the mRNA expression levels. Haynes states:

> "Interpretation of quantitative mRNA expression profiles frequently implicitly or explicitly assume that for specific genes the transcript levels are indicative of the levels of protein expression" (page 1863, left column, full paragraph 1),

Haynes goes on to state:

> "These results suggest that even for a population of genes predicted to be relatively homogenous ..., the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript" (page 1863, left column, full paragraph 1).

Haynes concludes that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript. Haynes provides evidence that protein expression levels are not predictable from the mRNA expression levels. Haynes cites this lack of predictability as one of the main reasons for proteome analysis to become an essential component in the comprehensive analysis of biological systems. Paragraph bridging pages 1862-1863; page 1863, left column, full paragraph 1. Haynes further teaches:

> "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis" page 1863, right column, full paragraph 2).

In view of the fact that protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript and the fact that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, the skilled artisan would not know if a change in the level of PRO1753 mRNA is associated with a corresponding change in the level of PRO1753 protein. Thus, Haynes supports the examiner's position that the skilled artisan would have a legitimate basis to doubt the utility of the PRO1753 polypeptide because the skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer. One skilled in the art would be required to do further research in order to determine whether or not the PRO1753 polypeptide levels changed significantly in the tumor samples. Such a further research requirement makes it clear that the

asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

Regarding the correlation of mRNA and protein expression levels, Gygi states:

> The correlation between mRNA and protein levels of the genes selected as described above is shown in Fig. 5. For the entire group (106 genes) for which a complete data set was generated, there was a general trend of increased protein levels resulting from increased mRNA levels. The Pearson product moment correlation coefficient for the whole data set (106 genes) was 0.935. This number is highly biased by a small number of genes with very large protein and message levels. A more representative subset of the data is shown in the inset of Fig. 5. It shows genes for which the message level was below 10 copies/cell and includes 69% (73 of 106 genes) of the data used in the study. The Pearson product moment correlation coefficient for this data set was only 0.356. We also found that levels of protein expression coded for by mRNA with comparable abundance varied by as much as 30-fold and that the mRNA levels coding for proteins with comparable expression levels varied by as much as 20-fold. Page 1726, left column, full paragraph 1.

Gygi goes on to state:

> We therefore expect that the correlation for all yeast proteins or for a random selection would be less than 0.4. The observed level of correlation between mRNA and protein expression levels suggests the importance of posttranslational mechanisms controlling gene expression. Such mechanisms include translational control and control of protein half-life. Since these mechanisms are also active in higher eukaryotic cells, we speculate that there is no predictive correlation between steady-state levels of mRNA and those of protein in mammalian cells. Page 1727, paragraph bridging left and right columns.

Gygi concludes:

> ... this study examined the relationship between yeast protein and message levels and revealed that transcript levels provide little predictive value with respect to the extent of protein expression. Page 1730, left column.

Haynes and Gygi, considered as a whole, teach that protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript and that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only

apparent by direct protein analysis. Thus, Haynes and Gygi support the examiner's position that the skilled artisan would not know if a change in mRNA level is associated with a corresponding change in protein levels and that the skilled artisan would have a legitimate basis to doubt the utility of the PRO1753 polypeptide because the skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer. Furthermore, the present specification only presents data showing a relative difference in PRO1753 mRNA levels between esophageal tumor and normal esophagus. There is no evidence that PRO1753 mRNA was highly expressed.

Applicants argue that it is not clear that Hancock supports the examiner's position because it appears that Hancock is arguing that proteomics has not developed sufficiently to be a reliable source of biomarkers. Applicants argue that Hancock offers very little support since it is an opinion with no accompanying references in a non-peer reviewed editorial. Applicant's arguments have been fully considered but they are not persuasive. Hancock is consistent with Haynes. Namely, the analysis of protein products is essential because protein expression levels are not predictable from the mRNA expression levels. One skilled in the art would be required to do further research in order to determine whether or not the PRO1753 polypeptide levels changed significantly in the tumor samples. Such a further research requirement makes it clear that the presently asserted utilities are not yet in currently available form, i.e., they are not substantial.

Applicants argue that a necessary correlation between mRNA and protein levels is not required to establish utility, but that there only need to be a reasonable correlation, that the references cited by the examiner support the notion that in general there is a positive correlation

between mRNA and protein levels, that all of the references cited by the examiner mention the usefulness of differential expression technology, which implies that there is a strong correlation between changes in mRNA and protein levels, that if there were no general correlation the skilled artisan would be focusing on differentially expressed proteins rather than differentially expressed genes, that if there were no general correlation differential analysis of mRNA would be useless. Applicant's arguments have been fully considered but they are not persuasive. The examiner can accept, for arguments sake, that gene expression analysis, tools or techniques have the potential for the discovery of new diagnostic or therapeutic targets. However, in the present case no information is provided in the differential analysis of PRO1753 mRNA expression regarding the level of expression, activity, or role in cancer of the PRO1753 polypeptide. The examiner does not agree that such a disclosure provides a "specific benefit in currently available form." This further characterization is part of the act of invention and until it has been undertaken, Applicants' invention is incomplete.

Applicants argue that they have established that the accepted understanding in the art is that there is a direct or reasonable correlation between the level of mRNA and the level of the encoded protein, as evidenced by paragraph 5 of the Grimaldi declaration (Exhibit 5), paragraph 6 of the Polakis declaration (Exhibit 6), as supported by the teachings in the Molecular Biology of the Cell, 3rd and 4th editions (Exhibits 7 and 8, respectively), as further supported by Lewin (Exhibit 9), and as additionally supported by Zhigang (Exhibit 10) and Meric (Exhibit 11) and that therefore it is more likely than not the skilled artisan would believe that, because the PRO1753 mRNA is more highly expressed in esophageal tumor as compared to normal esophagus, the PRO1753 polypeptide would also be more highly expressed in esophageal tumor

as compared to normal esophagus. Applicant's arguments have been fully considered but they are not persuasive. The declaration of J. Christopher Grimaldi under 37 CFR 1.132 filed 05/02/2005 (Exhibit 5) is insufficient to overcome the rejection of claims 4-8, 11-17 based upon a lack of utility as set forth in the last Office action because: Declarant argues that comparison of gene expression levels in normal versus diseased tissue has important implications, that two cell samples that have differing mRNA concentrations for a specific gene are expected to have correspondingly different concentrations of protein for that gene, that if the dogma that a change in mRNA will represent a similar change in protein did not hold true then techniques used to detect mRNA would have little value and not be so widely used, and that the detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment. Declarant's arguments have been fully considered but they are not persuasive. Firstly, the expression of all polynucleotides or polypeptides from a tumor sample or any other sample can invariably be classified as either increased, decreased, non-existent, or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are expressed in this manner can be used to detect or characterize the tumor or other sample. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility. Secondly, the examiner can accept, for arguments sake, that gene expression analysis, tools or techniques have the potential for the discovery of new diagnostic or therapeutic targets. However, in the present case no information is provided in the differential analysis of PRO1753 mRNA expression regarding the level of expression, activity, or role in cancer of the PRO1753 polypeptide. The examiner does not agree that such a disclosure provides a "specific benefit in currently available

form." This further characterization is part of the act of invention and until it has been undertaken, Applicants' invention is incomplete. The examiner is not saying that Applicants must disclose the activity or role in cancer of the PRO1753 polypeptide. The examiner is saying that Applicants have not provided any information in the present specification regarding the level of expression, activity, or role in cancer of the PRO1753 polypeptide. The present rejection is based upon Applicants' failure to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Unlike the situation in Grimaldi (Blood. 1989 Jun;73(8):2081-5), wherein chromosomal translocations have proven to be important markers of the genetic abnormalities central to the pathogenesis of cancer, there is no evidence that the present situation involves the cloning of a chromosomal breakpoint. Unlike the situation in Meeker (Blood. 1990 Jul 15;76(2):285-9), wherein serum IL-3 levels were measured and shown to correlate with disease activity, the present specification does not provide any testing of the level of expression, activity, or role in cancer of the PRO1753 polypeptide. Unlike the situation in Singleton (Pathol Annu. 1992;27 Pt 1:165-90), the present specification does not provide any testing of the level of expression, activity, or role in cancer of the PRO1753 polypeptide.

Declarant argues that even in cases where protein and mRNA expression do not correlate, this still provides significant information useful for cancer diagnosis and treatment because it enables more accurate tumor classification and hence better determination of a suitable therapy. Declarant's arguments have been fully considered but they are not persuasive. In effect, Declarant's position is that the disclosed PRO1753 mRNA, polypeptide, and antibodies are useful because those of skill in the art could experiment with them and figure out for themselves

what any observed experimental results might mean. The examiner does not agree that such a disclosure provides a "specific benefit in currently available form." This further characterization is part of the act of invention and until it has been undertaken, Applicants' invention is incomplete.

The declaration of Paul Polakis under 37 CFR 1.132 filed 05/02/2005 (Exhibit 6) is insufficient to overcome the rejection of Claims 4-8, 11-17 based upon a lack of utility as set forth in the last Office action because: Declarant states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Declarant states that antibodies to approximately 30 of the tumor antigen proteins have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in protein levels. Declarant states that an increased level of mRNA in a tumor cell relative to normal cell typically correlates to a similar increase in the encoded protein. Declarant states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. Declarant's arguments have been fully considered but they are not persuasive. The present application provides no information regarding the level of expression, activity, or role in cancer of the PRO1753 polypeptide. Only mRNA expression data was presented. The examiner has cited countervailing evidence to show: firstly, that the significance or relevance of the disclosed PRO1753 mRNA expression in relation to cancer

diagnosis or treatment is unknown; secondly, that protein levels are not always consistent with protein levels. Furthermore, the present specification provides no information regarding the level of expression, role or activity of the PRO1753 polypeptide in tumors. The present specification provides no information with which to determine whether PRO1753 mRNA or polypeptide expression in tumors would be important or would be attributable to tumor-independent differences between samples. One skilled in the art would not know if or how PRO1753 polypeptide expression would change in cancer. In the presence of evidence that the significance or relevance of PRO1753 mRNA expression in relation to cancer diagnosis or treatment is unknown, in the presence of evidence that protein levels are not always consistent with mRNA levels, and in the absence of any testing of the level of expression, role or activity of the PRO1753 polypeptide in tumors, the examiner concludes that there is no basis for concluding that the skilled artisan would be convinced that it is more likely than not that the PRO1753 polypeptide could be used for the diagnosis or treatment of cancer. Furthermore, a "dogma" is an authoritative principle, belief, or statement of ideas or opinion, especially one considered to be absolutely true. Haynes and Hancock provide evidence that Polakis's asserted dogma is not absolutely true and that the skilled artisan would have a legitimate basis to doubt the utility of the PRO1753 polypeptide based solely on the disclosure regarding DNA68883-1691 in Example 18 on page 143 of the present specification.

The teachings in the Molecular Biology of the Cell (Exhibits 7 and 8) and Lewin (Exhibit 9) are acknowledged. However, Molecular Biology of the Cell (Exhibit 7) acknowledges that "other controls can act later in the pathway from DNA to protein to modulate the amount of gene product that is made" (page 435, last full paragraph) and Lewin (Exhibit 9) acknowledges that

"production of RNA cannot inevitably be equated with production of protein" (paragraph bridging pages 847-848). Both Exhibits 7 and 9 support and are consistent with the examiner's position that the skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention.

It is acknowledged that Zhigang (Exhibit 10) presents data showing a high degree of correlation between PSCA protein and mRNA expression (page 4 of 7, right column, last sentence). However, exceptions were noted (paragraph bridging pages 3 of 7 and 4 of 7; page 4 of 7, left column, full paragraph 1). Thus, Zhigang supports and is consistent with the examiner's position that the skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention.

It is acknowledged that Meric (Exhibit 11) states that the "fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells" (page 971, right column, first paragraph of "Introduction"). However, the present specification does not provide any testing of the level of expression, activity, or role in cancer of the PRO1753 polypeptide. Therefore, the differences in PRO1753 polypeptide expression between cancer cells and normal cells are unknown, and thus not exploitable. Meric also acknowledges that several alterations in translational control occur in cancer (page 971, Abstract) and that gene expression is quite complicated (page 971, right column, first paragraph

of "Introduction"), suggesting that protein levels can be modulated independently of the level of mRNA. Thus, Meric supports and is consistent with the examiner's position that the skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention.

Applicants' discussion of Henikoff is acknowledged. However, Applicants are not relying on homology to establish utility of the PRO1753 polypeptide. Therefore, Henikoff is not germane to the asserted cancer diagnostics and therapeutics of the PRO1753 polypeptide insofar as Applicants are relying solely on the differential analysis of the PRO1753 mRNA expression for utility of the PRO1753 polypeptide. Nevertheless, Figure 110 shows various putative domains of SEQ ID NO: 110, and Henikoff provides evidence that one skilled in the art recognizes that although structural similarity can serve to classify a protein as related to other known proteins this classification is insufficient to establish a function or biological significance for the protein.

Applicants argue that the PRO1753 polypeptide and antibodies thereto would have diagnostic utility even if there is no direct correlation between gene expression and protein expression because the identification of both gene expression and protein expression enables more accurate tumor classification and better determination of therapy, as evidenced by the paragraph 6 of the Grimaldi declaration (Exhibit 5), as echoed by the Ashkenazi declaration (Exhibit 12), and as further supported by Hanna (Exhibit 13).

Applicant's arguments have been fully considered but they are not persuasive.

Paragraph 6 of the declaration of J. Christopher Grimaldi under 37 CFR 1.132 filed 05/02/2005 (Exhibit 5) is insufficient to overcome the rejection of claims 4-8, 11-17 based upon a lack of utility as set forth in the last Office action because: Declarant argues that even in cases where protein and mRNA expression do not correlate, this still provides significant information useful for cancer diagnosis and treatment because it enables more accurate tumor classification and hence better determination of a suitable therapy. Declarant's arguments have been fully considered but they are not persuasive. In effect, Declarant's position is that the disclosed PRO1753 mRNA, polypeptide, and antibodies are useful because those of skill in the art could experiment with them and figure out for themselves what any observed experimental results might mean. The examiner does not agree that such a disclosure provides a "specific benefit in currently available form." This further characterization is part of the act of invention and until it has been undertaken, Applicants' invention is incomplete.

The declaration of Dr. Ashkenazi under 37 CFR 1.132 filed 05/02/2005 (Exhibit 12) is insufficient to overcome the rejection of claims 4-8, 11-17 based upon a lack of utility as set forth in the last Office action because: Declarant asserts that amplification of certain genes gives cancer cells an advantage relative to normal cells. Declarant asserts that if the mRNA and gene product are over-expressed, then the gene product is a promising candidate for therapy. Declarant's arguments have been fully considered but they are not persuasive. The present claims are directed to or encompass the PRO1753 polypeptide (SEQ ID NO: 110). The present specification discloses that DNA68883-1691 is more highly expressed in esophageal tumor as compared to normal esophagus (page 143). However, no information is provided in the

differential expression of the PRO polypeptide-encoding nucleic acid data regarding the level of expression, activity, or role in cancer of the PRO1753 polypeptide.

Declarant asserts that a gene protein product of an amplified gene is useful regardless of the expression level of the protein because parallel monitoring of gene amplification and protein expression provides better tumor diagnosis, treatment, or classification. Declarant's arguments have been fully considered but they are not persuasive. The specification fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Rather than setting a de minimis standard, § 101 requires a utility that is "substantial", i.e., one that provides a specific benefit in currently available form. The examiner accepts for argument's sake that a person skilled in the art could derive some data regarding PRO1753 polypeptide expression in tumors in which PRO1753 mRNA is expressed. The examiner can also accept, for argument's sake, that such data could be used to correlate PRO1753 polypeptide expression with PRO1753 polynucleotide amplification or PRO1753 mRNA expression. The skilled artisan might also be able to derive a practical way of using this data. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicants' invention is incomplete. In effect, Declarant's position is that the PRO1753 polypeptide is useful because those of skill in the art could experiment with them and figure out for themselves what any observed experimental results might mean. The examiner does not agree that such a disclosure provides a "specific benefit in currently available form."

It is acknowledged that, in general, FISH and HIC results with HER-2/neu correlate well (Hanna, Exhibit 13). However, discordant results are seen and the significance of these results is

unclear (Hanna, first page, right column, last paragraph). Hanna states that HER-2/neu testing will utilize IHC as a screen, followed by FISH in IHC-negative cases (first page, right column, last paragraph), presumably to better understand the significance of these discordant results. This teaching does not provide a specific benefit in currently available form for the PRO1753 polypeptide. Therefore, in view of the evidence that protein levels are not always consistent with protein levels, Hanna supports the examiner's position that the differential expression analysis of DNA68883-1691 does not impute a specific, substantial, and credible utility to the PRO1753 polypeptide.

Applicants argue that the evidence of differential expression of the PRO1753 polynucleotide, along with the declarations, provide a specific utility for the PRO1753 polypeptides. Applicant's arguments have been fully considered but they are not persuasive. Applicants' have failed to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The skilled artisan would have a legitimate basis to doubt the utility of the PRO1753 polypeptide. Thus, the DNA68883-1691 expression data does not impute a specific and substantial utility to the polypeptide.

Applicants' conclusion regarding the utility of the claimed invention has been considered but it is not persuasive. In the present case, the disclosure that DNA68883-1691 is more highly expressed in esophageal tumor as compared to normal esophagus does not prove that the PRO1753 polypeptide will perform as a cancer diagnostic or therapeutic. The differential expression of the PRO1753 polynucleotide cannot be equated to and has not been adequately correlated with the contemplated cancer diagnostics or therapeutics of the claimed polypeptides.

The PRO1753 polypeptide has not been tested to the extent that utility would be known to those of skill in the art.

Claims 4-8, 11-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue that they have established a substantial, specific, and credible utility for the claimed polypeptides. Applicant's arguments have been fully considered but they are not persuasive. As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

Claims 4, 5, 12-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue that the skilled artisan would know how to make and use the claimed polypeptides. Applicant's arguments have been fully considered but they are not persuasive.

The limitation "wherein said isolated polypeptide is encoded by ... tissue" does not limit the claimed polypeptides.

Regarding the limitation "wherein said isolated polypeptide is more highly expressed ... tissue", no information is provided in the differential analysis of PRO1753 polynucleotide expression regarding the level of expression, activity, or role in cancer of the PRO1753 polypeptide. In the absence of this information a skilled practitioner would have to resort to a substantial amount of undue experimentation in the form of characterization of the PRO1753 polypeptide and validation of its association with lung tumors. It is this additional characterization of that single disclosed example of PRO1753 mRNA expression that is required in order for the skilled artisan to obtain the information necessary to practice the full scope of the claimed invention that constitutes undue experimentation. To the extent that Applicants rely on a central dogma, a significant probability, or reasonable correlation as discussed in their reply to the utility rejection, these arguments have been fully considered but they are not persuasive for the same reasons that they were not persuasive in the rejection for lack of utility. Specifically, the examiner has cited countervailing evidence to show that the skilled artisan would have a legitimate basis to doubt the utility of the PRO1753 polypeptide because the skilled artisan

recognizes that protein levels are not always consistent with mRNA levels. This evidence provides a reason for one skilled in the art to question the objective truth of the statement of diagnostic or therapeutic use of the claimed polypeptides. In the absence of any information on the role, activity, or expression of the PRO1753 polypeptide in cancer, the skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer. Therefore, the limitation "wherein said isolated polypeptide is more highly expressed ... tissue" does not enable the claimed invention.

Claims 14-17 recite the limitation "wherein said polypeptide ... can be used to generate an antibody ... ." These claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity, regardless of their biological activity. To obtain a valid patent, a patent application must be filed that contains a full and clear disclosure of the invention in the manner prescribed by 35 U.S.C. 112, first paragraph. The requirement for an adequate disclosure ensures that the public receives something in return for the exclusionary rights that are granted to the inventor by a patent. If mere antigenic cross-reactivity were the test for enablement under § 112, Applicants could obtain patent rights that may confer power to block off whole areas of scientific development related to the biologic activity of the polypeptide, for which Applicants have not provided any disclosure. It is entirely unclear why the disclosure of a single polypeptide, i.e., PRO1753, which is ideally suited to the making of antibodies to itself, would enable any and all antigenically cross-reactive polypeptides possessing the recited percent identity and possessing unknown and undisclosed biologic activities, when the specification provides no disclosure of any biological activity. Therefore, the scope of enablement provided to

the skilled artisan by the disclosure is not commensurate with the scope of protection sought by the claims.

Claims 4, 5, 12-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that based on the level of skill in the art, the cloning of PRO1753, the differential analysis of PRO1753 expression, the actual reduction to practice of SEQ ID NO: 109 and SEQ ID NO: 110, and the functional limitations, the skilled artisan would know that Applicants were in possession of the claimed invention. Applicant's arguments have been fully considered but they are not persuasive.

The limitation "wherein said isolated polypeptide is encoded by ... tissue" is a description of the nucleic acid molecule and does not describe the claimed polypeptides.

Regarding the limitation "wherein said isolated polypeptide is more highly expressed ... tissue", no information is provided in the differential analysis of PRO1753 polynucleotide expression regarding the level of expression, activity, or role in cancer of the PRO1753 polypeptide. The examiner has cited countervailing evidence to show that the skilled artisan would have a legitimate basis to doubt the utility of the PRO1753 polypeptide because the skilled artisan recognizes that protein levels are not always consistent with mRNA levels. This evidence provides a reason for one skilled in the art to question the objective truth of the

statement of diagnostic or therapeutic use of the claimed polypeptides. In the absence of any information on the role, activity, or expression of the PRO1753 polypeptide in cancer, the skilled artisan would not know if or how PRO1753 polypeptide expression would change in cancer. Therefore, the present disclosure does not reasonably convey to the skilled artisan that the present inventors had possession of the claimed invention. To the extent that Applicants rely on a central dogma, a significant probability, or reasonable correlation as discussed in the reply to the utility rejection in the last Office action, these arguments have been fully considered but they are not persuasive for the same reasons that they were not persuasive in the rejection for lack of utility and enablement.

Claims 14-17 recite the limitation "wherein said polypeptide ... can be used to generate an antibody ... ." These claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity, regardless of their biological activity. Applicants have not described the biologic activity of the PRO1753 polypeptide or any of its variants. It is entirely unclear why the disclosure of a single polypeptide, i.e., PRO1753, which is ideally suited to the making of antibodies to itself, would describe any and all antigenically cross-reactive polypeptides possessing the recited percent identity and possessing unknown and undisclosed biologic activities, when the specification does not describe any biological activity. Therefore, the claimed subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Because the specification does not describe any biological activity of the claimed polypeptides and because the claims are not

limited to any specific biologic activity of the claimed polypeptides, the present claims are not analogous to example 14 of the written description guidelines.

Regarding other U. S. Patents that may have issued containing claims to variant polynucleotides and polypeptides, suffice it to say that each case must be decided on its own merits based on the evidence of record.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

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DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
JULY 24, 2005